REMARKS

Claims 1-5 remain pending for prosecution in this application.

Applicants note with appreciation the withdrawal of the various rejections/objections as noted by the Examiner on pages 2-3 of the present Office Action.

Applicants have amended the specification as suggested by the Examiner to remove therefrom the browser-executable code.

The Rejections under 35 U.S.C. § 101

Claims 1-5 stand rejected under 35 U.S.C. § 101 as allegedly not being supported by either a specific and substantial asserted or a well-established utility. The general basis of the Examiner's rejection is that the data presented in Example 18 of the present specification is insufficient to establish a patentable utility for the presently claimed subject matter. Applicants respectfully traverse the rejection.

A. The Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility".

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed. However, when the condition to be diagnosed is specifically identified, the asserted utility is "specific".

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in Brenner v. Manson, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the

"substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. § 2107.01, emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility".

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible". "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. § 2107 II (B)(1)(ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The PTO also sets forth the evidentiary standard as to utility rejections. In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); In re Irons, 340 F.2d 974, 144 USPQ 351 (1965); In re Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

B. The Data At Issue

The data at issue in the present Office Action is that which is presented in Example 18 starting on page 140 of the current specification. Example 18 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay which allows one to quantitatively measure the level of gene expression for any gene in any sample of mRNA or cDNA produced from that mRNA. Moreover, as described in Example 18, a β-actin control is employed to ensure that the total amount of nucleic acid in all samples being tested is the same. Since use of the β-actin control assures that all tested samples contain the same amount of total nucleic acid and since the assay allows one to quantitatively measure the amount of expression for any specific gene of interest, the assay allows one to make clear, concise and reproducible quantitative comparisons of "gene-specific" expression between two of more samples. In other words, the assay allows one to detect quantitative differences in gene expression between two or more different samples. Therefore, using this assay, one can determine whether any gene of interest is expressed at a higher or lower rate in a sample derived from a first tissue of interest (say, for example, a cancerous tumor tissue) than in a second tissue of interest (say, for example, a normal tissue).

It is exactly this type of comparison that is presented in Example 18 for the polypeptide-encoding nucleotide sequence referred to in the present specification as DNA59610-1556. More specifically, the data in Example 18 demonstrate that there is a detectable difference in DNA59610-1556 expression in:

(a) at least one type of human lung tumor when compared to its normal human lung tissue counterpart (detectably higher expression in the tumor than in the corresponding normal tissue);

(b) at least one type of human esophageal tumor when compared to its normal human esophageal tissue counterpart (detectably higher expression in the tumor than in the corresponding normal tissue); and

(c) at least one type of human melanoma skin tumor when compared to its normal human skin tissue counterpart (detectably lower expression in the tumor than in the corresponding normal tissue).

Based upon these data, Applicants have asserted in the present patent application that this reproducible, quantitative difference in the level of expression of DNA59610-1556 can be exploited for diagnosing the presence of a particular type of lung, esophageal and/or melanoma tumor in a human subject. More specific to the presently claimed invention, the antibodies claimed herein find use as diagnostic tools for determining the presence of certain types of human lung, esophageal and melanoma tumors.

Contrary to the Applicants assertion of utility herein, however, the Examiner alleges that the differential gene expression described in Example 18 does not render the presently claimed antibodies patentably useful. Applicants respectfully submit, however, that upon application of the appropriate legal standards described above, the proper conclusion is that the present application does disclose a patentable utility for the claimed invention.

In support of the outstanding rejection, the Examiner first asserts:

> "[t]issue-specific expression such as that found in Example 18 is not specific to the polynucleotide encoding the polypeptide of SEQ ID NO:60. It does not depend on any characteristic of the nucleic acid molecule itself." (see the Office Action at page 4, lines 2-4).

Applicants are not sure that they understand this argument. As described above, the "specificity" requirement for an asserted utility under 35 U.S.C. § 101 merely requires a patent applicant to set forth and describe the asserted utility with specificity. Applicants have herein asserted that the claimed invention is useful diagnostically and has also specifically identified and described the diseases for which the invention is diagnostically useful. This is clearly sufficient to satisfy this requirement.

Notwithstanding Applicants' confusion as to exactly what the Examiner is arguing in the quote presented above, however, it is possible that the Examiner means that while DNA59610-1556 may be differentially expressed in certain types of lung, esophageal and melanoma tumors as compared to their normal counterpart tissues, there may be other unrelated genes which exhibit the same differential expression pattern and, therefore, the data is not "specific" to the DNA59610-1556 molecule. Applicants, however, believe this argument to be flawed for a variety of reasons. First, the Examiner's statement that the differential gene expression profile described for DNA59610-1556 is "not specific to the polynucleotide" is completely unsupported. The Examiner provides no example of any other molecule which exhibits the same differential gene expression profile as DNA59610-1556. As such, Applicants respectfully submit that the Examiner has failed to establish even a *prima facie* case supporting her argument.

Secondly, even if the Examiner did provide an example of an unrelated polynucleotide that possessed identical differential gene expression characteristics (such that this expression profile was not "specific" to DNA59610-1556), that still would not render the presently claimed invention unpatentable for lack of utility. To the contrary, one would expect both molecules to be patentable because they are both useful, even though they are useful for the same thing. In other words, it is well established that valid patents can issue independently on two different compositions that are useful for the same thing (e.g., patents can issue to both compounds A and an unrelated compound B, even though both compounds A and are useful for, for example, diagnosing the presence of the same disease).

In short, Applicants describe for the first time in the present application that a specifically identified human gene (called DNA59610-1556 herein) is differentially expressed in certain human tumors as compared to their corresponding normal human tissue. This differential expression profile can be exploited for the purpose of diagnosing the presence of those tumors as described in detail in the present application, regardless of whether there may be another molecule which may be useful for the same thing. As such, the Examiner's argument that the differential tissue expression data presented in Example 18 of the above captioned patent application is "not specific" to DNA59610-1556 and "does not depend on any characteristic" of DNA59610-1556 simply does not render the presently claimed invention unpatentable for lack of utility.

In further support of the outstanding rejection, the Examiner next asserts:

> "[i]n Example 18, the specification merely states that the gene is 'more highly expressed' in one tissue as compared to another. There is no guidance in the specification as to how high the levels are.....[t]he only thing Applicants teach is that the gene was 'more highly expressed', and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases." (see the Office Action at page 4, lines 8-18, emphasis supplied).

Applicants strongly disagree. The two important aspects about the DNA59610-1556-related data presented in Example 18 are (1) there is a detectable difference in DNA59610-1556 gene expression between the various tumor samples tested and their normal respective counterparts, and (2) the level of expression of DNA59610-1556 is detectably higher in the lung and esophageal tumors tested than in the corresponding normal lung and esophageal tissues, respectively, and detectably lower in the melanoma tumors tested then in the corresponding normal skin tissues. The Examiner seems to focus on "how much higher" or "how much lower" (i.e., requiring Applicants to provide exact numbers), but Applicants submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful. What is important for the diagnostic utility asserted in the present application is (1) to be able to quantitatively compare the level of DNA59610-1556 expression in a tumor sample to a normal sample and (2) to detect a relative difference in the level of gene

expression between the tumor and normal samples. The exact magnitude or size of that difference is irrelevant to the utility.

For example, the asserted utility relies only upon being able to detect a relative difference in the level of DNA59610-1556 expression in the tumor sample as compared to the normal sample...the exact magnitude thereof is not relevant. Thus, if one employs the described assay to quantitatively compare the level of DNA59610-1556 expression in, for example, (i) an human esophagus-derived tissue sample of unknown pathology and (ii) a corresponding normal human esophageal tissue sample, one of two results will be obtained. First, the investigator may find that the level of DNA59610-1556 expression in the unknown sample as compared to the known normal sample is either the same or detectably lower. In this case, no useful diagnostic information is obtained. However, if the investigator finds that the level of DNA59610-1556 expression is detectably higher in the sample of unknown pathology as compared to known normal sample, then useful diagnostic information is obtained. Therefore, contrary to the Examiner assertion quoted above, knowledge of the fact that DNA59610-1556 is "more highly expressed" in one tissue as compared to another does "enable the skilled artisan to differentiate amongst expression levels" and, as such, does provide useful diagnostic information.

Finally, in support of the outstanding rejection, the Examiner asserts:

> "[t]here is no information in the specification as to the type of tumors, malignant or benign, that are affected. Applicants do not provide any evidence that indicates....whether the results were statistically significant. Applicants have provided no indication of the nature of the number of samples that were used. The art teaches that individual changes may be associated with clonal expansion, which would not be characteristic of the class of tumors as a whole (see, for example, Bover et al., 1998, Cell. Mol. Biol. 44(3):493-504)." (see Office Action at page 4, lines 10-15).

In response, Applicants first wish to point out that the Examiner is making an incorrect assumption about what Applicants are claiming as utility for the claimed invention. It appears that the Examiner believes that Applicants are claiming that the observed and herein described differential expression profile of DNA59610-1556 is diagnostic for all lung, esophageal and melanoma tumors. In fact, this

is clear in that the Examiner focuses on things such as "what types of tumors were tested", "how many tumors were tested" and "were the numbers sufficiently high to provide statistically significant results", etc. This assumption, however, is patently incorrect. Applicants do not in any way assert that the observed and herein described differential expression profile of DNA59610-1556 is diagnostic for all lung, esophageal and melanoma tumors. In fact, Applicants are unaware of the existence of any diagnostic test that is capable of doing that. To the contrary, Applicants merely claim that the observed and herein described differential expression profile of DNA59610-1556 is diagnostic for the presence of (i) only those lung and esophageal tumors that exhibit detectable overexpression of DNA59610-1556 as compared to the corresponding and respective normal tissue type and (ii) only those melanoma tumors that exhibit detectable underexpression of DNA59610-1556 as compared to the corresponding normal tissue type. This provides a clear and currently available benefit to the public.

For example and for purposes of clarification, it is clear that the data presented in Example 18 and described above demonstrates that the expression of DNA59610-1556 is upregulated in at least one type of lung tumor and at least one type of esophageal tumor as compared to the normal corresponding tissue. As such, as described above, an investigator may employ the assay described in Example 18 to quantitatively compare the level of DNA59610-1556 expression in, for example, (i) a human esophageal-derived tissue sample of unknown pathology, but which is suspected of being an esophageal tumor, and (ii) a known normal human esophageal tissue sample. If the investigator finds that the levels of DNA59610-1556 expression in the two tissue samples are not detectably different, then that information is not diagnostically useful. On the other hand, however, if the investigator finds that the level of DNA59610-1556 is detectably and reproducibly higher in the sample of unknown pathology as compared to the sample of normal pathology, then useful diagnostic information is clearly obtained. Since Applicants are not asserting a "general" diagnostic utility for the entire class of all human lung tumors, or all human esophageal tumors, or all human melanoma tumors, there is no need to test and provide data for numerous different types of human

lung, esophageal or melanoma tumors, nor is there a need to demonstrate "statistical significance" across a wide range of different tumor types. As such, a currently existing benefit to the public does exist.

In summary, therefore, the utility asserted herein is "specific" in that it describes a clear diagnostic utility and furthermore describes the specific disease conditions associated with that utility, i.e., those human lung, esophageal and melanoma tumors exhibiting aberrant expression of DNA59610-1556 as compared to normal. Moreover, the utility asserted herein is "substantial" in that it provides a "currently available benefit to the public". In this regard, as described above, the legal standards for utility under 35 U.S.C. § 101 require that "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility'" (see, M.P.E.P. § 2107.01, emphasis supplied). Finally, the utility asserted herein is "credible" in that the data presented in Example 18 of the current specification clearly shows that DNA59610-1556 is (i) detectably upregulated in at least one type of human lung and esophageal tumor when compared to the corresponding and respective normal tissue, and (ii) detectably downregulated in at least one type of human melanoma tumor when compared to the corresponding normal tissue. Thus, while the data presented in the present application and described in detail herein may not necessarily provide a diagnostic test for the presence or absence of all lung-, esophageal- and melanoma-derived tumors (in fact, Applicants believe that such a test may not ever exist), it does provide a diagnostic test for at least a subset of those.....and that is all that is required to satisfy the requirements of 35 U.S.C. § 101.

As a final note, Applicants wish to comments on the Bover et al. article cited by the Examiner in the present Office Action. This article merely teaches that alterations in the level of gene amplification at the genomic DNA level may occur during clonal expansion of cells derived from a primary tumor, for example, when those cells are expanded through multiple generations of growth *in vitro*. These teachings are completely irrelevant to the issue at hand as the above described

diagnostic utility has nothing to do with detecting amplification of segments of genomic DNA. Moreover, as described in Example 18, the samples being tested are derived from the primary tumors themselves and, as such, there is no issue with regard to clonal expansion in, for example, *an in vitro* system.

In light of the above, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

The Rejection under 35 U.S.C. § 112, First Paragraph

Claims 14-16 stand rejected under 35 U.S.C. § 112, first paragraph, as the claimed invention is allegedly not supported by a specific or substantial utility and, therefore, the Examiner asserts that the specification fails to teach "how to use" the claimed invention. Applicants respectfully traverse the rejection.

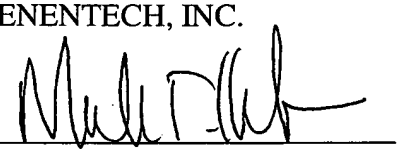
In this regard, Applicants refer to the arguments and information presented above in response to the outstanding rejection under 35 U.S.C. § 101. Applicants respectfully submit that as described above, the presently claimed invention is supported by a specific, substantial and credible utility and, therefore, the present specification teaches one of ordinary skill in the art "how to use" the claimed invention without undue experimentation as described above. As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

In light of the above amendments and remarks, Applicants believe that this application is now in condition for immediate allowance and respectfully request that the outstanding rejections be withdrawn and this case passed to issue.

The Examiner is invited to contact the undersigned at (650) 225-4461 if any issues may be resolved in that manner.

Respectfully submitted,

GENENTECH, INC.

By: 

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